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EXAMINER
FOSTER, CHRISTINE E

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1641	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/711,517	ABBOTT ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11 and 13-41* is/are pending in the application.

4a) Of the above claim(s) *24-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-11 and 13-23* is/are rejected.

7)☒ Claim(s) *3,6-9,13,14,18 and 21* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *9/23/04* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/12/2007 has been entered.

2. Claims 1, 3, 6-9, 13-14, and 18 were amended. Claims 1-11 and 13-41 are pending in the application, with claims 24-41 currently withdrawn.

3. Applicant is reminded of the proper format for amendments to the claims:

Applicant must use the status identifier (currently amended) if the claims are being amended.

Specifically, it is noted that claim 8 is accompanied by the status identifier (Original), yet the claim text includes markings indicating that the claim has been amended.

In addition, all claims being currently amended must be presented with markings to indicate the changes that have been made relative to the immediate prior version.

However, in line 1 of claim 8, the numeral "5" has apparently been replaced by the numeral "6" but there are no markings to denote the insertion of the numeral "6" in the claim.

See CFR 1.121 and MPEP 714.

Objections/Rejections Withdrawn

4. The objection to the specification regarding sequence compliance is withdrawn in light of Applicant's submission of a new computer readable form (CRF) for the sequence listing on 9/11/2006.

5. The objections to the drawings are withdrawn in light of Applicant's submission of new copies of Figures 4.2 and 6.2.

6. The objection to claim 23 has been obviated by the amendments to claim 1.

7. The rejections of claims 1-13 and 15-23 under 35 USC 103(a) as being unpatentable over Bernard et al. in view of Abbot et al. (US 6,852,285) have been withdrawn in favor of the rejections set forth below over Bernard et al. or Renault et al. in view of Abbott et al. (US 6,284,197, of record), which issued from a continuing application as that of US 6,852,285 but which has an earlier issue date.

8. The rejections of claims 1-11 and 13-23 under 35 USC 112, 2nd paragraph not reiterated below have been withdrawn.

Claim Objections

9. Claims 3, 6-9, 13-14, 18, and 21 are objected to because of the following informalities:

10. Claim 3 recites "a nucleic acid analogs" in line 4, which lacks proper subject-verb agreement.

11. Claim 6 is objected to because it recites that the PDMS affinity substrate is "terminated by a peptide moiety". The claim is objected to because it would seem that the peptide moiety corresponds to the "receptors" that are recited in claim 1; however, this is not made clear in the

claim. As a result, the claim is confusing because the role of the peptide moiety in the method of claim 1 is unclear.

Claims 7-9 are also objected to for similar reasons because they fail to make clear that the "peptide moiety" or "antibody" is the receptor referred to in claim 1.

12. Claim 8 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 8 recites that "the peptide moiety" (of claim 6) is an "antibody". Applicant has not provided a specific definition for the term "peptide" in the specification. However, this term is normally understood in the art to refer to amino acid polymers of less than 100 residues (see the attached definitions of the term "peptide", downloaded from http://www.xreferplus.com on 3/21/2007). See also, for example, Feldenstein (US 5352461), at column 6, lines 6-9; and Steiner et al. (US 6652885), at column 5, lines 3-5. Since antibodies are larger than 100 residues, they would not be considered to be "peptides" according to the normal definition of this term. Therefore, the recitation that the peptide moiety is an antibody is improper because it broadens, rather than further limits, the parent claims.

13. Claim 13 recites "wherein the each receptor", which is objected to for grammatical reasons. The claim should apparently read --wherein each of the receptors-- or similar terminology.

14. Claim 14 refers to "the receptors **in** the affinity substrate" (emphasis added), which is unclear because while claim 1 refers to an affinity substrate **comprising** an array of receptors,

there is no prior indication in the claims that the receptors are contained **in** the affinity substrate. Clarification is requested.

15. Claims 18 and 21 objected to because the text appears to be single-spaced, while the text of other claims appears to be double-spaced. The use of one and one-half or double spaced lines is required. See 37 CFR 1.52(b).

Claim Rejections - 35 USC § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 1-11 and 13-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

18. Claim 1 as amended recites the step of "detecting the presence of the ligand on the detection surface using a detection substrate having a liquid crystal". The claim as originally filed recited detecting the ligand on the detection surface, "wherein the detection surface further comprises a liquid crystal". The currently claimed invention now involves the use of a "detection substrate" that separately recited from the "detection surface". This would suggest that the "detection surface" may be distinct from the "detection substrate", i.e., that the "detection substrate" is a separate component or part.

where the "detection surface" is distinct from the "detection substrate", i.e., where the "detection substrate" is a separate component or part.

However, the specification apparently uses the terms "detection surface" and "detection substrate" synonymously; see especially [0019], [0030], [0061], [0106]. There is no clear distinction made between a "detection surface" and "detection substrate" in the specification.

Specifically, the specification discloses that a liquid crystal is placed on the detection surface after it has been contacted with the affinity substrate (see page 15, [0061]). In this embodiment, the "detection surface" would be one and the same as the "detection substrate", since there is only one surface/substrate used. However, the currently claimed invention is broader in scope that this embodiment, since by separately reciting a "detection surface" and a "detection substrate", the claims imply that the two may be separate components.

The specification also a second embodiment where that the detection surface can be part of a liquid crystal assay cell. The liquid crystal is sandwiched between two substrates, one of which is the detection surface [0063] and [0154]. However, the instant claims do not recite that the detection surface is one of the two substrates of a liquid crystal assay cell.

As such, the amended claims are broader in scope than either of these two disclosed embodiments, being drawn generically to methods "using a detection substrate having a liquid crystal". There is no generic disclosure in the specification of methods of detecting the presence of a ligand on a detection surface "using a detection substrate having a liquid crystal". In the currently claimed methods, the "detection substrate" could be construed to be a separate part from the "detection surface". The only disclosure reading on this would be the embodiment using a

two-substrate liquid crystal assay cell in which one of the substrates is the detection surface. However, the claims are not limited to this embodiment.

Applicant indicates that the amendments are supported at [0024]-[0027] and at [0090]-[0107] and states that no new matter has been added (Reply, p. 13). Paragraphs [0024]-[0027] as indicated by Applicant do not provide adequate written description of the currently claimed methods. It is noted that the only place that a "detection substrate" is mentioned is at [0027], where it is apparently used synonymously as the "detection surface". Paragraphs [0090]-[0107] as indicated by Applicant also apparently use the terms "detection surface" and "detection substrate" synonymously. There is no indication in the noted passages that the "detection substrate" is a separate part or component from the "detection surface".

In summary, the amendments broaden the scope of the disclosure and claims as originally filed with respect to the claimed detection step, and therefore represent new matter.

19. Claim 1 now recites a method for detecting "at least one ligand" using an affinity substrate that comprises an array of receptors, wherein each receptor is capable of specifically bind to "a ligand."

The claims as originally filed recited that the affinity substrate may comprise an array of receptors (see original claim 12) that may have specificity for more than one ligand, thereby allowing detection of more than one ligand (see original claim 13).

Similarly, the specification also discloses at [0019] that:

> In another embodiment, the method provides the affinity substrate comprising an array of receptors located in distinct locations. Generally, the receptors in the array have specificities for more than one ligand such that the liquid crystal is capable of detecting presence of more than one ligand.

However, claim 1 as amended is not limited to ***an array of receptors that have specificity for more than one ligand***. Since the claim recites only that the receptors are capable of specifically binding to "a ligand", this would also encompass different receptors that have specificity for the same ligand as well as for different ligands.

This represents a departure from the specification and claims as originally filed because the only method of detecting more than one ligand that is described in the specification is that involving an array of receptors that have specificities for more than one ligand. The claiming of a method of detecting "more than one ligand" without the accompanying limitation of an array of receptors with specificity for more than one ligand represents a broadening amendment not supported by the original disclosure and claims. One skilled in the art cannot envisage possession of all methods of detecting multiple ligands encompassed by the claims based on the limited disclosure of using an array of receptors with specificities for more than one ligand, when the claims are not so limited.

20. Claims 1-11, 13, and 15-23 also represent new matter for the following reasons. As noted above, the recitation of an array of receptors capable of specifically binding to "a ligand" would encompass scenarios in which multiple, different receptors all having specificity for ***the same ligand*** are used, which represents a departure from the specification and claims as originally filed. Such scenarios are not generically described in the specification; there is no general teaching regarding the use of different receptors having specificity for the same ligand.

Applicant indicates that support may be in the specification at [0181], in which four specific antibodies (111.6, anti-PY1068, anti-PY1114, and anti-PY1173) were arrayed in order

to detect phosphorylated EGFR (see Applicant's Reply of 5/19/06, p. 16-17 and the instant Reply at p. 10).

However, one skilled in the art would not envisage possession of all methods involving different receptors all having specificity for the same ligand based on this limited example; the showing in the example is not commensurate with the scope of the claims. The claims are not limited to methods in which the specific antibodies 111.6, anti-PY1068, anti-PY1148, and anti-PY1173 are used as receptors to detect the ligand EGFR, but rather encompass all sets or arrays of receptors having specificity for any ligand.

Applicant is effectively claiming a new subgenus that is not described in the specification. The reliance on a single or limited species does not provide sufficient direction and guidance to the features currently claimed. It cannot be said that a subgenus is necessarily described by a genus encompassing it and a species upon which it reads. See In re Smith 173 USPQ 679, 683 (CCPA 1972) and MPEP 2163.05.

Although the specific antibodies disclosed in the example may all happen have specificity for the same ligand (EGFR in this case), such an example fails to convey evidence of possession since the specification never clearly draws the skilled artisan's attention to this property; the concept of the currently claimed genus of receptors having specificity for the same ligand is never introduced.

The specification fails to generically describe the genus of methods involving arrays of different receptors each having specificity for the same ligand that is now claimed. At best, the example of [0181] may represent a species reading on the claimed genus as a consequence of inherent properties of the four specific antibodies used. However, this specific example fails to

provide support for the claimed genus since such inherent properties are never clearly pointed out. The relevant identifying characteristic of the claimed genus is simply not mentioned in the specification. One skilled in the art would not envisage possession of a genus when the concept of the genus is never introduced in the specification. The fact that the antibodies used in the example may represent a species reading on that genus is not enough to support the genus since the characteristics that identify the members of the genus are not described in the specification.

21. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

22. Claims 1-11 and 13-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

23. Claim 1 recites the limitation "the ligand" in lines 6-10. There is insufficient antecedent basis for this limitation in the claims because the claims refer to a sample having or suspected of having "a ligand" in line 3, but also to receptors that are capable of binding to "a ligand" in line 5. The preamble also refers to detecting "at least one ligand". Since there may apparently be more than one "ligand", and because the claims do not require that the ligand(s) in the sample be the same as the ligand(s) to which the receptors specifically bind, the references to "the ligand" are indefinite since it is unclear which ligand(s) is being referred to.

24. For these same reasons, the recitation of "the ligand" in claim 9 also lacks proper antecedent basis.

25. Claim 1 recites the limitation "the receptor" in lines 6 and 8. There is insufficient antecedent basis for this limitation in the claims because the claims refer to an "array of receptors" and not to a receptor *per se*. Since the "array of receptors" could include any array of different types of receptors, the recitation of "the receptor" is indefinite because it is unclear which receptor is being referred to.

26. Where applicant acts as his or her own lexicographer to specifically define a term of a claim contrary to its ordinary meaning, the written description must clearly redefine the claim term and set forth the uncommon definition so as to put one reasonably skilled in the art on notice that the applicant intended to so redefine that claim term. *Process Control Corp. v. HydReclaim Corp.*, 190 F.3d 1350, 1357, 52 USPQ2d 1029, 1033 (Fed. Cir. 1999). The term "**peptide moiety**" in claims 6-8 is used by the claim to encompass "antibody", while the accepted meaning is "**a series of less than 100 amino acids**." The term is indefinite because the specification does not clearly redefine the term.

Claim 8 recites that "the peptide moiety" (of claim 6) is an "antibody". Applicant has not provided a specific definition for the term "peptide" in the specification. However, as noted above, this term is normally understood in the art to refer to amino acid polymers of less than 100 residues (see the attached definitions of the term "peptide", downloaded from http://www.xreferplus.com on 3/21/2007). See also, for example, Feldenstein (US 5352461), at column 6, lines 6-9; and Steiner et al. (US 6652885), at column 5, lines 3-5. Since antibodies are larger than 100 residues, they would not be considered to be "peptides" according to the normal definition of this term. Therefore, the recitation of a "peptide moiety" is indefinite because Applicant has not clearly redefined the term "peptide" in such a way so that it would encompass

antibodies. Given the non-standard use of the term "peptide", the metes and bounds of the claims are unclear.

27. Claim 13 recites the limitation "the receptor-bound ligand". There is insufficient antecedent basis for this limitation in the claims because as noted above, claim 1 refers to multiple receptors and ligands. As such, the claim is indefinite because it is unclear which receptor-ligand pair is being referred to. The reference to "the receptor-bound ligand" also lacks antecedent basis because although claim 1 recites contacting the sample with the receptors, the claim does not explicitly recite a step in which the ligand(s) is actually bound to the receptors.

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

30. Claims 1-6, 8-11, 13, 15-20 and 22-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over either Bernard et al. ("Affinity capture of proteins from solution and their dissociation by contact printing" (2001) *Nature Biotechnology* **19**:866-869) or alternatively over Renault et al. (*Agnew. Chem. Int. Ed.* 2002, 41, No. 13, 2320-2323, Applicant's IDS of 1/30/2006 and the Supporting Information for the article obtained from http://www.angewandte.org on 3/21/07) in view of Abbott et al. (US 6,284,197 B1, Applicant's IDS of 1/30/2006).

Bernard et al. teach a method for detecting at least one ligand comprising (a) contacting a sample having a ligand ("target molecules", for example ^{125}I-IgG) with an affinity substrate (polydimethylsiloxane (PDMS) stamp), wherein the affinity substrate comprises an array of receptors that are capable of specifically binding a ligand. The receptors are referred to as "capturing molecules", and can be for example anti-mouse IgGs, which are capable of specifically binding to a ligand (for example IgG). See entire selection, in particular the abstract; Figures 1-2 and p. 866, left column and the paragraph bridging the left and right columns; and p. 869, "Derivatization of stamps".

The plurality of receptors that are covalently immobilized on the affinity substrate would be considered an "array" as claimed since there are multiple receptor molecules immobilized to the affinity substrate as depicted for example in Figure 1; each receptor molecule is capable of capturing molecules. Alternatively, the multiple teeth of the PDMS stamp would also be considered to define an array of receptors, since the regions of receptors immobilized on the various teeth would be considered to be an "array" or pattern of the receptors. In addition, the reference also teaches that the affinity substrate could be patterned with various different types of

capturing molecules in order to screen for several ligands in a parallel manner (see the paragraph bridging pages 868-869). Such "smart stamps" would also be considered to have an "array" of the various types of receptors.

Bernard et al. further teach (b) contacting the affinity substrate with a detection surface (glass or polystyrene), wherein at least a portion of the ligand that is bound to the receptor is transferred to the detection surface (see in particular p. 866, left column, second paragraph; p. 867, left column; Figure 3; the first paragraph of "Results and Discussion" on p. 866; and also p. 869, "Affinity stamping").

Bernard et al. differs from the claimed invention in that it fails to specifically teach detecting the presence of the ligand using a detection substrate *having a liquid crystal*, wherein a change in the orientation of the liquid crystal indicates the presence of a ligand. In Bernard et al., the printed ligands are detected using radioactive or fluorescent labels attached to the target ligands (see especially p. 866, right column; p. 869, right column; and Figures 2 and 4).

Like Bernard et al., Renault et al. similarly teaches an affinity capture method followed by microcontact printing. In particular, Renault et al. teaches a method for detecting at least one ligand ("target molecules", for example antibodies) by contacting a sample (e.g., solution containing target antibodies) with an affinity substrate (PDMS elastomeric stamp) (see entire selection, especially p. 2320, left column and the paragraph bridging the left and right columns; p. 2323, left column, last paragraph; and Figures 1, 2d, and 3-4). The affinity substrate comprises an array of receptors ("capture molecules") on the substrate, defining various capture sites that each have different capture molecules capable of specifically binding to different target proteins

(see depiction in Figure 1A; p. 2321, right column and also p. 2320, the paragraph bridging the left and right columns).

Renault et al. further teach contacting the affinity substrate with a detection surface ("substrate", which was glass in the examples); see also p. 2322, left column. This results in the captured target molecules being transferred onto the substrate (see depiction in Figure 1E).

However, like Bernard et al., the teachings of Renault et al. differ from the claimed invention in that the reference fails to specifically teach detecting the presence of the ligand using a detection substrate *having a liquid crystal*, wherein a change in the orientation of the liquid crystal indicates the presence of a ligand. As in Bernard et al., detection of the presence of the ligand on the detection surface was performed using labeled target molecules: Renault et al. teaches detection of fluorescent- or gold-labeled antibodies by fluorescence microscopy or atomic force microscopy, respectively (see especially Figure 5).

Abbott et al. teach devices and methods for detecting a ligand based on the use of liquid crystals to amplify and transduce into an optical signal the interaction of a wide array of molecules with various surfaces (see entire selection, in particular the abstract). In particular, the reference teaches liquid crystal devices comprising one or more substrates as well as a liquid crystal (mesogens), which undergo a detectable switch in orientation upon interaction of the ligand and receptor, allowing for the ligand to be detected. The use of liquid crystals in the detection surface of Abbott et al. obviates the need for prelabeling of ligand, such as with a radiolabel or a fluorescent moiety (see column 5, lines 5-10).

The devices can be used in methods for detecting ligands ("analytes"), wherein the ligand is first contacted with a substrate that contains a receptor ("recognition moiety") for the analyte

to form a complex. The ligand is then contacted with a detection surface ("substrate"), wherein at least a portion of the ligand is transferred to the detection surface, and its presence on the detection surface is detected using a liquid crystal (see column 5, line 13 to column 6, line 3; column 13, lines 3-31; column 14, lines 15-43; column 20, lines 4-12; column 38, line 46 to column 39, line 50). The liquid crystals (mesogens) undergo a detectable switch in orientation upon interaction, allowing for the ligand to be detected.

Therefore, it would have been obvious to one of ordinary skill in the art to use the device of Abbott et al. (substrate comprising a liquid crystal) as the detection surface on which the ligand is microcontact printed and to detect the ligand by a change in orientation of the liquid crystal in the methods for detecting a ligand of either Bernard et al. or Renault et al. One would be motivated to do this because Abbott et al. teach that liquid crystal detection surfaces do not require prelabeling of the ligand (as was performed in Bernard et al. and Renault et al.); as such, one would be motivated to stamp the affinity-captured ligand onto the device of Abbott et al. in order to avoid the need for using fluorescent or other labels on the ligands. One would have reasonable expectation of success in affinity stamping the surface of Abbott et al. according to the method of Bernard et al. or Renault et al. because the surface of Abbott et al. is compatible with microcontact printing (see column 17, lines 5-22).

With regard to claim 2, Bernard et al. teach (a) washing the affinity substrate after the contacting step (a) above (p. 869, "Affinity stamping"). Renault et al. also teach (a) rinsing the stamp after contacting it with the sample (see especially the legend to Figure 2).

With regard to claims 4-5, Bernard et al. teach affinity substrates consisting of PDMS as an inert elastomer (p. 866, left column, paragraph 3). Renault et al. also teaches a PDMS elastomeric stamp (see especially p. 2320, left column).

With respect to claims 6 and 8-9, the PDMS affinity substrates of Bernard et al. are "antibody-terminated" in that the antibodies are attached to the ends of PDMS stamps (Figure 1). The antibodies are capable of binding to a protein (^{125}I-IgG). Bernard et al. teach the use of antibodies in this context as capturing molecules (e.g., see p. 866, first two paragraphs of "Results and Discussion"). Similarly, Renault et al. teach attaching the capture molecules (which may be antibodies) to the surface or end of the PDMS stamps (Figure 1 and p. 2320-2321).

With regard to claim 10, Bernard et al. teach that the antibodies, protein A, and streptavidin were applied to the affinity stamps via the cross-linker BS3 (p. 869, "Derivatization of stamps"). Renault et al. similarly teach that the receptors are attached via this same crosslinker (p. 2320, right column).

With regard to claim 11, while not specifically recited by Bernard et al., the amount of ligand present in the sample was necessarily quantified because Bernard et al. teach the concentrations of the ligands TRITC-labeled rabbit IgG and biotinylated alkaline phosphatase in the samples (see p 869, "Affinity Stamping and Figure 2A). Similarly, Renault et al. report the quantity of the ligand in the sample (see Supporting Information, page 1), such that the ligand was necessarily quantified.

With regard to claims 15-17 and 19, Abbott et al. further teach that the detection surface may comprise self-assembled monolayers in order to anchor the liquid crystal mesogenic layer, where the self-assembled monolayers may be formed from alkanethiols or organosulfur

compounds and may comprise amines through functionalization (the abstract; column 19, line 25 to column 21, line 16). Abbott et al. teach that use of certain self-assembled monolayers enables homeotropically anchoring of mesogens, and that homeotropic anchoring is the most preferred anchoring direction (see especially column 18, line 4, to column 19, line 45). Abbott et al. teach that the detection surface may be treated with 1-aminododecanoic acid to make the surface surface-active (column 25, lines 26-31).

With regard to claim 18, the specification discloses that "The method comprises the steps of: (a) contacting the ligand to a first surface, wherein the ligand is at least in part attached to the first surface; (b) contacting the ligand-decorated first surface to a second surface, wherein the ligand is at least in part attached to the second surface, *such that at least a portion of the first surface is partially curved"* (paragraph 28, emphasis added). Thus, the specification indicates that partial curvature of the affinity substrate occurs as a result of contacting the affinity substrate with a surface. In the absence of any specific structural limitations recited, the methods of Bernard et al. or Renault et al. and Abbott et al. meet the claim since in the course of contacting the affinity substrates of Bernard et al. or Renault et al. with the detection surface of Abbott et al., the surface of the affinity substrates would become partially curved as indicated by the specification.

With regard to claims 20 and 22, the liquid crystal mesogens of Abbott et al. may be thermotropic or lyotropic and may be nematic, chiral nematic, smectic, frustrated liquid crystals, or discotic liquid crystals (column 30, line 30 to column 32, line 29), and a preferred liquid crystal is 4-cyano-4'-pentylbiphenyl (5CB) (column 37, lines 53-59).

With regard to claim 23, Abbott et al. teach that the detection surface allows for optical detection of orientation of the liquid crystal (mesogens), which allows for ease of detection (column 5, lines 13-26). Electrical detection may also be employed (column 38, lines 56-63).

31. Claims 7 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bernard et al. or Renault et al. in view of Abbott et al. as applied to claim 1 above, and further in view of Tang et al. (US Patent No. 5,886,195).

As discussed above, Bernard et al. teaches PDMS stamps that comprise a plurality of IgG receptors, and also teach stamps patterned with various types of receptors. The liquid crystal detection surface of Abbott et al. is capable of detecting the presence of more than one ligand. However, the references fail to specifically teach a method wherein the receptors are capable of detecting the presence of protein phosphorylation in EGFR residues, or wherein the PDMS stamp is terminated with a peptide moiety capable of binding to a phosphorylated ligand.

Tang et al. teach anti-phosphotyrosine antibodies, which may be used to measure autophosphorylation of EGFR and thereby an increase in EGF activity (column 6, lines 53-65).

Therefore, it would have been obvious to one of ordinary skill in the art to employ the anti-phosphotyrosine antibodies taught by Tang et al. as the capturing molecules on the PDMS affinity substrates in the method for detecting a ligand of Bernard et al. and Abbott et al., or alternatively of Renault et al. and Abbott et al. in order to measure autophosphorylation of EGFR. Note that this teaching reads on claim since Applicant is employing the term "peptide moiety" so as to encompass antibodies. One would have reasonable expectation of success

because Bernard et al. and Renault et al. teach that antibodies can be used as capture molecules on PDMS stamps.

32. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bernard et al. or Renault et al. in view of Abbott et al. as applied to claim 1 above, and further in view of Choi et al. (US 6,292,296).

Bernard et al., Renault et al., and Abbott et al. are as discussed above, which fail to treat a method wherein a liquid crystal is pretreated by illumination with UV light.

Choi et al. teach methods for aligning liquid crystal devices, including rubbing as well as photo-alignment using ultraviolet light (column 1, lines 10-51). The reference teaches that compared with the rubbing method, there is no electrostatic discharge or dust particles associated with photo-alignment, thus obviating low yield problems.

Therefore, would have been obvious to one of ordinary skill in the art at the time of the invention to prepare the liquid crystal detection surface of Abbott et al. by photo-alignment with ultraviolet light as taught by Choi et al., rather than by rubbing as taught in the reference, in the method of Bernard et al. (or Renault et al.) and Abbott et al. order to align the liquid crystal detection surface while avoiding disadvantages such as dust particles that are associated with the rubbing method.

Double Patenting

33. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

34. Claims 1-11 and 13-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-23 of copending Application No. 11/542,432 in view of Renault et al.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '432 application also claims a method for detecting a ligand (analyte) in which an affinity substrate ("affinity stamp") is used to transfer a captured analyte from the stamp to a detection surface ("substrate surface") by microcontact printing (see especially claims 18-19). Although the '432 application fails to specifically recite that the affinity substrate is contacted with a sample having or suspected of having the ligand, such a step would be immediately envisaged since the claims recite a method of detecting an analyte *in a sample.* The '432 application further recites the step of detecting the presence of the ligand by detecting a change or departure in the orientation of the liquid crystal (see especially claims 18 and 22-23).

The '432 application differs from the claimed invention in that it fails to specifically recite that the affinity substrate comprises an array of receptors, wherein each receptor is capable of specifically binding to a ligand.

However, Renault et al. teaches methods of transferring captured analytes from affinity stamps by affinity microcontact printing. The reference teaches assembling an "array" of various types of capturing molecules on the surface of a stamp (see especially Figure 1 and p. 2320, the paragraph bridging the left and right columns). The reference teaches that this allows simultaneous capture of different target proteins from a complex solution (ibid).

Therefore, it would have been obvious to one of ordinary skill in the art to provide the affinity stamp of the '432 application with an array of receptors in order to enable simultaneous capture of different target proteins from a complex solution.

35. Claims 1-11 and 13-23 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-34 of copending Application No. 11/418,755 in view of Renault et al.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the '755 application also claims a method for detecting the presence of an analyte in a sample suspected of containing the analyte by exposing the sample with an affinity substrate (stamp comprising a pad functionalized with a ligand) and then contacting the affinity substrate with a detection surface ("detection region") (see especially claim 21). The presence of the analyte on the detection region is determined by detecting a change in the orientation ("ordering") of a liquid crystal (see also claim 34).

The '755 application differs from the claimed invention in that it fails to specifically recite that the affinity substrate comprises an array of receptors, wherein each receptor is capable of specifically binding to a ligand.

However, Renault et al. teaches methods of transferring captured analytes from affinity stamps by affinity microcontact printing. The reference teaches assembling an "array" of various types of capturing molecules on the surface of a stamp (see especially Figure 1 and p. 2320, the paragraph bridging the left and right columns). The reference teaches that this allows simultaneous capture of different target proteins from a complex solution (ibid).

Therefore, it would have been obvious to one of ordinary skill in the art to provide the affinity stamp of the '432 application with an array of receptors in order to enable simultaneous capture of different target proteins from a complex solution.

The above are provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Response to Arguments

36. Applicant's arguments filed 1/12/2007 have been fully considered.

37. With respect to the rejection of claim 13 under 35 USC 112, 1st paragraph (new matter), Applicant's arguments (see pages 9-12) have been fully considered but they are not persuasive for reasons of record.

The claim as originally filed recited that the receptors in the array have specificities for more than one ligand, i.e., for different ligands. As amended, claim 1 (and claim 13) recites that each receptor has specificity for "a ligand". This represents a broadening amendment, as it would

scenarios such as the above but also scenarios where the receptors all have specificity for the *same* one ligand.

Applicant is arguing that such scenarios are supported in the specification at [0181] by the disclosure of the specific antibodies 111.6, anti-PY1068, anti-PY1114, and anti-PY1173 (see Reply, page 10). Applicant argues in effect that the four antibodies inherently have specificity for the same one ligand (phosphorylated EGFR), and that therefore, the claims do not represent new matter because they reflect inherent properties.

However, the showing in the example is not commensurate with the scope of the claims. Inherent properties of the specific four disclosed antibodies cannot support claim limitations that pertain to all receptors. Whether or not the four specific antibodies possess the inherent property of having specificity for the same ligand is immaterial, since the claims are much broader in scope. The claims are not limited to the specific antibodies 111.6, anti-PY1068, anti-PY1148, and anti-PY1173 as receptors, but rather are drawn to all receptors having specificity for any ligand. In order to establish adequate written description of the currently claimed invention based on inherent properties, Applicant would need to establish that all receptors necessarily and always have specificity for the same ligand; this has not been done.

Although the specific antibodies disclosed in the example may all have specificity for the same ligand (EGFR in this case), such an example fails to convey evidence of possession since the specification never clearly draws the skilled artisan's attention to this feature; the concept of the currently claimed genus involving receptors having specificity for the same ligand is never introduced.

In regards to the Office's contention that the limited example disclosed at [0181] involving the specific antibodies noted above is not commensurate with the scope of the claims, Applicant argues that each antibody is capable of binding its ligand independently of the other antibody, and that therefore, they cannot be considered a single species (see Reply, the paragraph bridging p. 11-12). Applicant also argues that each recognizes a different "ligand" in that each recognizes a different epitope or residue on EGFR. Such arguments are not persuasive since the example in which the four antibodies (receptors) were used to detect a single ligand (EGFR) as disclosed at [0181] represent a single example or species reading on the claimed method; the fact that multiple reagents are involved is immaterial. Even if one were to accept Applicant's arguments that the four specific reagents represent four species reading on the claimed genus rather than none, it is nonetheless clear that the scope of the claims is nonetheless much broader than the example of [0181], which is not limited to these four antibodies or to detection of EGFR as a ligand. The limited teachings are not commensurate with the claim scope because they do not reflect

In summary, the specification fails to disclose the genus of methods involving arrays of different receptors each having specificity for the same ligand that is now claimed. Although the example of [0181] may represent an example reading on the claimed genus as a consequence of inherent properties of the four specific antibodies used in that example (specificity for the same ligand), the specific example fails to provide support for the claimed genus since such inherent properties are never clearly pointed out. One skilled in the art would not envisage possession of a genus when the concept of the genus is never introduced in the specification. The fact that the antibodies used in the example may represent a species reading on that genus is not enough to

support the genus since the characteristics that identify the members of the genus are not described in the specification.

38. With respect to the rejection of claim 1 under 35 USC 112, 2nd paragraph regarding lack of antecedent basis for "the receptor", Applicant argues (see page 12) that the rejection has been obviated by the amendments to recite "a receptor" including two or more receptors of different specificity...". However, the amended claim does not include the recitation indicated by Applicant. The rejection is maintained for the reasons set forth in the rejection above.

39. With respect to the rejections of claims 1-11 and 13-23 as being unpatentable over Bernard et al. in view of Abbott et al. (US 6,852,285), the examiner notes that the rejections have been withdrawn in favor of the above rejections over either Bernard et al. or Renault et al. in view of Abbott et al. (US 6,284,197 B1). The Abbott et al. '285 reference and the Abbott et al. '197 reference contain the same teachings since the application from which the '285 reference issued is a continuation of the application from which the '197 application issued; however, the '197 patent is now being applied because it has an earlier issue date. Applicant's arguments regarding the '285 patent will be addressed below as they are equally applicable to the instant rejections over the '197 patent.

Applicant argues (see pages 17-23) that there is no motivation to combine the references (p. 18), which is not persuasive for reasons of record as noted in the rejection. Specifically, the Abbott et al. reference teaches that the use of liquid crystals allows for detection of analytes without the need for prelabeling.

Applicant argues that because Bernard et al. teach that the transfer of captured molecules to the detection surface may seem "counter-intuitive," the reference teaches away from the

claimed invention (p. 18). Such arguments are unpersuasive since Bernard et al. make this comment in the context of mentioning that while transfer of the captured ligand may seem counterintuitive *in introducing their results*, their results as described in the publication clearly show that this is indeed what occurs. Thus, the fact that the authors suggest that their findings might be initially counterintuitive (i.e., prior to a full reading of the reference), when the reference is read as a whole, such a comment does not teach away from the clear and repeated teachings throughout the reference that captured molecules are indeed transferred, as taught for example in the title of the reference.

Applicant further argues that Bernard et al. only teach the method for the field of cell biology and cell culture, and not to the identification of ligands as described in Abbott et al. (see p. 18-19). This is not found persuasive Bernard et al. clearly teach that the affinity printing method should have "general applicability" (see p. 868, right column). Further, as noted in the rejection, the reference teaches the *detection of ligands on a surface*, which is the same purpose for which the detection surface of Abbott et al. is employed (see for example the abstract of Abbott et al.).

Applicant further argues that there is no motivation to combine the references and quotes extensively from the '285 patent (see pages 19-20). However, the relevance of these passages are not fully understood as they pertain to the rejection since Applicant has not explained how the noted teachings of the '285 patent would lead to the conclusion that there is no motivation to combine the references.

Applicant further argues (see pages 20-22) that microcontact printing is described in Abbott et al. only in a general sense, and that the reference does not teach the steps of

transferring a ligand/target to a liquid crystal-prepared surface. Applicant also argues that Bernard et al. does not teach a detection surface that is reusable or that is composed of liquid crystals (pages 22-23). Such arguments amount to a piecemeal analysis of the references. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). In the instant case, the Bernard et al. reference was relied upon for teaching the steps of inking and transferring a ligand to a surface by microcontact printing. Furthermore, even if Abbott et al. teach microcontact printing in another sense, such a teaching is nonetheless relevant to the instant rejection since it establishes that the detection surface of Abbott et al. is compatible with microcontact printing, such that one would have a reasonable expectation of success in applying the ligand to the detection surface of Abbott et al. by the microcontact printing method of Bernard et al.

Applicant further argues that there is no reasonable expectation of success because the combination of Bernard et al. and Abbott et al. would not yield the claimed method (Reply, pages 20-22). However, this argument is not persuasive because Applicant has not pointed to any claimed elements or method step in particular that is missing from the combination.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "reusable" detection surface; see pages 22-23) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

In response to applicant's argument that the references do not identify the advantages of the present invention (see page 24), the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Applicant does not separately argue the limitations of the dependent claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 8:30-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached at (571) 272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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